Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

Molecular characterization of *Candida auris* outbreak isolates in Qatar from patients with COVID-19 reveals the emergence of isolates resistant to three classes of antifungal drugs

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ABSTRACT

Objectives: During the COVID-19 pandemic in Qatar, many patients who were severely ill were colonized and infected by *Candida auris*, an invasive multidrug-resistant yeast pathogen that spreads through nosocomial transmission within healthcare facilities. Here, we investigated the molecular epidemiology of these *C. auris* isolates and the mechanisms associated with antifungal drug resistance.

Methods: Whole genomes of 76 clinical *C. auris* isolates, including 65 from patients with COVID-19 collected from March 2020 to June 2021, from nine major hospitals were sequenced on Illumina NextSeq. Single nucleotide polymorphisms were used to determine their epidemiological patterns and mechanisms for antifungal resistance. The data were compared with those published prior to the COVID-19 pandemic from 2018 to 2020 in Qatar.

Results: Genomic analysis revealed low genetic variability among the isolates from patients with and without COVID-19, confirming a clonal outbreak and ongoing dissemination of *C. auris* among various healthcare facilities. Based on antifungal susceptibility profiles, more than 70% (22/28) of isolates were resistant to both fluconazole and amphotericin B. Variant analysis revealed the presence of multi-antifungal resistant isolates with prominent amino acid substitutions: Y132F in *ERG11* and V704L in *CDR1* linked to reduced azole susceptibility and the emergence of echinocandin resistance samples bearing mutations in *FKS1* in comparison with pre-COVID-19 pandemic samples. One sample (CAS109) was resistant to three classes of antifungal drugs with a unique premature stop codon in *ERG3* and novel mutations in *CDR2*, which may be associated with elevated amphotericin B and azole resistance.

Discussion: Candida auris isolates from patients with COVID-19 and from most patient samples without COVID-19 in Qatar were highly clonal. The data demonstrated the emergence of multidrug-resistant strains that carry novel mutations linked to enhanced resistance to azoles, echinocandins, and amphotericin B. Understanding the epidemiology and drug resistance will inform the infection control strategy and drug therapy. **Fatma Ben Abid, Clin Microbiol Infect 2023;▪:1**

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Introduction

Candida species are the leading etiological agents of invasive candidiasis, which is associated with significant morbidity and mortality [1–3]. *Candida auris* is an emerging multidrug-resistant yeast pathogen of serious global concern [3,4]. Since 2009, *C. auris* has caused nosocomial bloodstream infections in numerous countries in South Asia, North and South Americas, East Asia, the Middle East, Africa, and Europe [4–7]. Considering its ability to tolerate temperatures up to 42 °C and the capacity for persisting in the hospital environment and causing person-to-person transmission [4], this yeast causes outbreaks in many hospitals [5].

Of particular concern, a significant rise in *C. auris* infections was observed during the COVID-19 pandemics [8–10]. SARS-CoV-2 infection alters immune and metabolic responses in patients, which together produce an inflammatory environment that is highly permissive to fungal infections [10]. Fungal co-infections, such as invasive candidiasis, among patients with COVID-19 have been reported, and these infections are likely to increase mortality [10,11]. Many patients with COVID-19 infection needed intensive care unit (ICU) admission. These patients are at higher risk of developing invasive candidiasis due to prolonged ICU stays, presence of central venous catheter, use of systemic corticosteroid therapy, and the use of broad spectrum antibiotics [9,11,12]. In Qatar, around 5–10% of patients with COVID-19 require admission to ICU [13,14].

Candida auris infections in Qatar were reported prior to 2020, and the strains belonged to the South Asia lineage (clade 1) [15,16]. Nosocomial infection within the healthcare facilities and travelling migrant workers could be the major route of transmission and introduction [15,17]. As part of the ongoing surveillance and pre-hospitalization screening, additional *C. auris* isolates were identified, mostly from patients with COVID-19. The aim of this study was to characterize *C. auris* isolates obtained during COVID-19 pandemic period in Qatar and to compare their molecular epidemiology with those isolated prior to the COVID-19 pandemic using the whole genome sequencing approach. Also, we characterized the mutations in genes that are associated with reduced susceptibility to antifungal drugs such as azoles, amphotericin B and echinocandins.

Methods

During the COVID-19 pandemics, *C. auris* samples were isolated and identified by matrix-assisted laser desorption/ionization-time of flight mass spectrometry, and the antifungal susceptibility testing (AST) was performed. DNA was extracted, and DNA libraries were sequenced on Illumina NextSeq 550 platform. Bioinformatics analyses were performed too (Supplementary Data).

The study was approved by the hospital ethics committee (IRB #2019-0009). This was a retrospective, non-interventional study and only required a collection of previously generated data; informed consent was not required.

Results

We sequenced 76 *Candida auris* genomes (CAS53–CAS131), of which 65 were from patients with COVID-19 and the rest were from sporadic infections. The samples included 42 screening specimens, 14 blood, 13 urinary, four respiratory, and three wound specimens (Table S1). All patients with blood and wound infections had previously received echinocandins, fluconazole, or amphotericin B (AMB) treatment prior to *C. auris* detection (Table S1). Less than 50% of patients colonized with *C. auris* in the respiratory system (2/5, 40%), urinary tract (6/13, 46%), and other body sites (18/42, 43%) had received antifungal treatments (Table S1).

Antifungal susceptibilities were evaluated for 28 isolates; 24 were evaluated by Sensititre YeastOne, while four were evaluated by Vitek2. Fluconazole MICs were above the CDC breakpoint of ≥32 mg/L for all isolates, except two having MICs of 16 mg/L. Eleven (39%) and seven (25%) isolates had higher MICs to ≥2 and ≥3 azoles, respectively (Table 1). Twenty-two isolates (79%), including one measured using Vitek2, were resistant to amphotericin B (MIC ≥2 mg/L), while three isolates (CAS109, CAS112, CAS129) were resistant to three echinocandin; for instance, CAS109 was resistant to caspofungin, anidulafungin, and micafungin (MIC = 8 mg/L) (Table 2). More than 70% (20/28) of the isolates were resistant to both fluconazole and amphotericin B, while CAS109 was resistant to all three classes of antifungal drugs.

In this study, 5057854 to 11973588 high-quality reads were generated for each sample (Table S1). A single nucleotide polymorphism (SNP) tree revealed a low level of genetic heterogeneity among the isolates collected from nine healthcare institutions in this investigation (Fig. S1). Among the 76 isolates, 57 isolates were collected from patients from ICU, 49 from medical wards, and 15 from long-term care units (Table S1). Of the patients reviewed, 19 had records of transfer within and among healthcare facilities (Table S1). To reveal the relationship between the isolates collected prior to and during the pandemics, we generated a tree containing 122 samples in Qatar (Fig. 1), including those published by Salah et al. [15] in 2021. Within the major circulating clones containing 115 isolates from outbreaks, sporadic and environmental samples, the genetic difference was very small (range, 0–21 base pairs). The high degree of sequence similarity among isolates within and among major tertiary health care institutions supported the widespread *C. auris* transmission and dissemination in Qatar. Also, all 76 isolates in this study clustered together in the major group and cannot be differentiated from the predominant “circulating clone” defined since 2021 (Fig. 1). However, the phylogenetic tree indicated the presence of a few subgroups within the circulating clone; for instance, CAS109 was clustered with CAS46, CAS86, and CAS73.

Based on variant annotation of current and previous Qatari *C. auris*, 120 isolates had known azole-linked resistance amino acid substitutions Y132F and E709D in *ERG11* (B9J08_001448) and *CDR1* (B9J08_000164), respectively (Table 2). *FKS1* (B9J08_000964) hotspot substitutions associated with echinocandin resistance were detected in CAS129 and CAS112 (S639F) and CAS109 (S639Y). A unique mutation resulting in a stop codon (E68*) in *ERG3* (B9J08_003737) was detected in CAS109, and a novel missense substitution (L1124P) in *CDR2* (B9J08_002451) was reported in CAS46, CAS73, CAS86, and CAS109 (Table 2). In fact, compared with clade 1 reference genome B8441 (GCA_002759435.2), all Qatari isolates possessed amino acid substitution M192I in *ERG4* (B9J08_002852), K74E in *CIS2* (B9J08_003232), K52N and E1464K in *SNQ2* (B9J08_001125), as well as a silent substitution (A870C) in *ERG5* (B9J08_004161) (Table 2). In addition, all isolates had substitution K719N in the *STE6* (B9J08_002389) gene, an *a*-pheromone ABC family transporter that showed antimycotic responses [17]. In addition, we observed undocumented SNPs/insertions and deletions (indels) in *TAC1b* (B9J08_004820) from the non-COVID-19 outbreak *C. auris* isolates reported in the early investigation [15] (Supplementary Data).

Discussion

COVID-19 pandemics have resulted in an unprecedented public health crisis [9,10]. Among the patients with COVID-19 who need medical care in the ICU in Qatar, the risk of developing bloodstream *Candida* infection was higher in older patients and in those who

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Table 1
In vitro susceptibility to antifungal agents in *Candida auris* isolates (CAS1 and CAS52 were characterized in 2021). Elevated minimum inhibitory concentration (MIC) values are bold.

ID	Date of isolation	Hospital	Specimen	AMB	FLC	ITC	POS	VOR	5Fc	CASP	ANI	MICA	Method	COVID-19	Antifungals
Current study															
CAS55	20/06/2020	Hamad General Hospital	Blood	**2**	**128**	16	8	8	0.12	**8**	0.25	0.12	YO	Yes	ANI, AMB
CAS57	07/08/2020	Hamad General Hospital	Blood	**2**	**64**	0.06	0.03	0.25	0.12	0.25	0.06	0.12	YO	Yes	CASP
CAS58	12/08/2020	Rhumailah long term facility	Urine	**2**	**64**	0.06	0.015	0.25	0.12	0.25	0.06	0.12	YO	Yes	ANI
CAS59	15/08/2020	Hazm Meberik Hospital	Respiratory	**2**	**64**	0.12	0.015	0.25	0.12	0.25	0.25	0.12	YO	Yes	FLC
CAS69	21/08/2020	Hazm Meberik Hospital	Blood	1	**64**	0.06	0.03	0.12	0.12	0.12	0.12	0.06	YO	Yes	ANI, CASP
CAS67	28/08/2020	Hazm Meberik Hospital	Screening	**2**	**64**	0.12	0.015	0.25	0.12	0.25	0.12	0.12	YO	Yes	Nil
CAS73	10/09/2020	Hamad General Hospital	Screening	**8**	**32**	NA	NA	≤0.12	≤1	≤0.12	NA	≤0.06	Vitek	No	FLU
CAS77	24/09/2020	Hamad General Hospital	Blood	**2**	**128**	0.25	0.12	8	0.25	0.25	0.12	0.12	YO	Yes	ANI
CAS86	08/11/2020	Hamad General Hospital	Screening	**8**	**16**	NA	NA	≤0.12	≤1	≤0.12	NA	≤0.06	Vitek	No	Nil
CAS87	06/12/2020	Hamad General Hospital	wound	**2**	**128**	0.25	0.06	1	0.06	0.25	0.12	0.12	YO	Yes	FLU, ANI
CAS109	25/12/2020	Hamad General Hospital	wound	**2**	**128**	16	8	8	0.25	**8**	**8**	**8**	YO	No	ANI
CAS105	08/03/2021	Hazm Meberik Hospital	Blood	**2**	**128**	8	8	8	0.12	0.12	0.25	0.12	YO	Yes	ANI
CAS130	08/03/2021	Hamad General Hospital	Urine	**2**	**128**	1	0.25	8	0.12	0.25	0.12	0.12	YO	No	Nil
CAS107	14/03/2021	Hamad General Hospital	Urine	1	**128**	0.5	0.12	8	0.06	0.5	0.25	0.12	YO	No	ANI
CAS123	01/04/2021	Hamad General Hospital	Blood	**2**	**64**	0.12	0.03	0.25	0.12	0.25	0.12	0.12	YO	Yes	FLU, ANI
CAS112	13/04/2021	Hamad General Hospital	Urine	**2**	**64**	0.06	0.015	0.25	0.12	**8**	**4**	**8**	YO	Yes	ANI
CAS111	14/04/2021	Hamad General Hospital	Urine	**4**	**128**	16	8	8	0.12	0.25	0.12	0.12	YO	Yes	Nil
CAS113	22/04/2021	Hamad General Hospital	Urine	**4**	**128**	1	1	1	0.12	0.25	0.25	0.12	YO	Yes	Nil
CAS115	24/04/2021	Hamad General Hospital	Respiratory	1	**128**	16	2	8	0.12	0.25	0.12	0.12	YO	Yes	Nil
CAS119	06/05/2021	Hazm Meberik Hospital	Blood	**2**	**128**	1	0.12	8	0.12	0.12	0.12	0.12	YO	Yes	ANI
CAS129	07/05/2021	Hazm Meberik Hospital	Urine	**2**	**32**	0.06	0.015	0.12	0.12	**2**	**8**	**8**	YO	Yes	FLU, ANI
CAS126	08/05/2021	Hazm Meberik Hospital	Urine	1	**128**	0.12	0.03	0.5	0.12	0.03	0.12	0.06	YO	Yes	ANI
CAS116	11/05/2021	Hamad General Hospital	Urine	**4**	**128**	16	8	8	0.12	**8**	0.25	0.25	YO	No	Nil
CAS124	18/05/2021	Hazm Meberik Hospital	Blood	1	**128**	0.12	0.03	0.5	0.06	0.12	0.12	0.12	YO	Yes	ANI
CAS131	19/05/2021	Hamad General Hospital	Blood	**2**	**128**	16	8	8	0.12	0.5	0.25	0.12	YO	Yes	ANI
CAS121	29/05/2021	Hazm Meberik Hospital	Blood	0.5	**32**	NA	NA	≤0.12	≤1	≤0.12	NA	≤0.06	Vitek	Yes	FLU, CASP
CAS120	31/05/2021	Hazm Meberik Hospital	Blood	**≥16**	**16**	NA	NA	0.25	≤1	0.25	NA	≤0.06	Vitek	Yes	ANI
CAS127	05/06/2021	Hazm Meberik hospital	Blood	**4**	**32**	0.25	0.06	0.5	0.12	0.25	0.12	0.12	YO	Yes	ANI
Previous study (re-measured)															
CAS1	21/12/2018	Al-Wakra Hospital	Respiratory	**8**	**16**	NA	NA	≤0.12	≤1	≤0.12	NA	≤0.06	Vitek	No	NA
CAS52	25/08/2020	Hamad General Hospital	Screening	**8**	**16**	NA	NA	≤0.12	≤1	≤0.12	NA	≤0.06	Vitek	No	ANI, CASP

AMB = amphotericin B; FLC = fluconazole; ITC = itraconazole; POS = posaconazole; VOR = voriconazole; 5Fc = flucytosine; CASP = caspofungin; ANI = anidulafungin; MICA = micafungin; NA = not available; YO = Sensititre YeastOne.

have a more severe critical illness [13]. In fact, most documented cases of *C. auris* in 2020–2021 in Qatar were reported in patients with COVID-19. Our data indicated a sustained, clonal outbreak of *C. auris* during the pandemic, as all 76 isolates collected during the pandemics period were highly similar (Fig. S1). During the pandemics, many patients with COVID-19 were severely ill and hospitalized, as they required respiratory support. *Candida auris* infections associated with patients with COVID-19 have been reported in the USA, India, Pakistan, Oman, and other countries [14,18]. Most patients in Qatar did not travel or did not seek medical care elsewhere during the lockdown and prolonged period of travel restriction (Table S1), suggesting that the infections were acquired from within the country and the healthcare facilities were the reservoir of this pathogen [6]. The prolonged hospital stay could favour the exposure and colonization of *C. auris*.

Our study confirmed the high degree of clonality among the *C. auris* outbreak isolates [19,20], as the pairwise SNP differences were small (1–21 base pairs) among 76 isolates from nine major tertiary hospitals (Table S1). In addition, there was no clear differentiation between isolates from patients with and without COVID-19. Isolates recovered from blood, urine, respiratory specimens, and sterile sites of patients in different wards of different healthcare facilities clustered with isolates collected in 2019 and 2020 (Fig. 1). In contrast, genetic variability has been reported in the pre–COVID-19 pandemics *C. auris* isolates, in which migrant workers and medical care overseas may play a key role in the introduction of *C. auris* within our facilities [15].

Candida auris continues to spread globally, and most isolates belong to the four major clades. In 2018, the first clade 5 isolate was identified in a patient who had no travel history, and it was susceptible to all three classes of antifungals [7,21,22]. There was a recent report of multiple clade 5 isolates collected in Iran [21]. However, all *C. auris* isolates identified in Qatar belong to the South Asian clade 1, similar to those identified in Kuwait, Oman, UAE, and Saudi Arabia [23–26].

Our study has identified known mutations in several genes involved in conferring resistance to echinocandins and azoles. Echinocandin resistance is often associated with *FKS1* hotspot mutations. Three *C. auris* isolates bearing S639F or S639Y showed higher MIC values (≥2 mg/L, up to 8 mg/L) to caspofungin, anidulafungin, and micafungin compared with the susceptible isolates. These mutations were also reported in other investigations [4,27]; S639F substitution in *FKS1* was discovered in four pan-echinocandin–resistant samples out of 39 isolates sequenced in India [24]. In Kuwait, five out of 32 isolates that originated from eight patients contained S639F in *FKS1*; two other isolates contained a D642Y or S639P mutation [25]. In addition, all seven isolates with *FKS1* mutations were recovered from urine [25], and two of our *FKS1* mutants were also from urine, suggesting that urine samples may develop resistance to echinocandins more easily [25]. In terms of fluconazole resistance, substitutions in *ERG11* (Y132F) and *CDR1* (E709D) are common in South Asian clade 1 isolates [27–29]. These mutations may cause cross-resistance to other azoles [30]. *TAC1b* is a transcription factor controlling *CDR1* expression in *Candida* species, and mutations in *TAC1b* were associated with increased azole resistance [28,31]. During the variant analysis, both known and undocumented SNPs/indels were detected in *TAC1b* (B9J08_004820) in Qatari isolates; amino acid substitution A640V was previously reported in samples CAS17 and CAS20 [15] (Table 2). Substitutions A583S, A640V, and S192N in *TAC1b* have been reported in previously

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Table 2
List of common and unique variants reported in *Candida auris* in Qatar.

Gene	GeneID	Mutations/Substitution	Substitution	Variant	Samples (combined current study and Salah et al. 2021)
Common					
CIS2	B9J08_003232	c.220A>G p.Lys74Glu	K74E	missense_variant	all 122 isolates
ERG4	B9J08_002852	c.576G>T p.Met192Ile	M192I	missense_variant	all 122 isolates
ERG5_1	B9J08_004161	c.870A>C p.Thr290Thr	T290T	synonymous_variant	all 122 isolates
SNQ2	B9J08_001125	c.156A>T p.Lys52Asn	K52N	missense_variant	all 122 isolates
		c.4390G>A p.Glu1464Lys	E1464K	missense_variant	all 122 isolates
STE6	B9J08_002389	c.2157G>T p.Lys719Asn	K719N	missense_variant	all 122 isolates
Unique					
CDR1	B9J08_000164	c.2110G>T p.Val704Leu	V704L	missense_variant	CAS20 and CAS17
		c.2127A>T p.Glu709Asp	E709D	missense_variant	remaining 120 isolates
CDR1_1	B9J08_002451	c.3371T>C p.Leu1124Pro	L1124P	missense_variant	CAS46, CAS73, CAS86, and CAS109
ERG11	B9J08_001448	c.428A>G p.Lys143Arg	K143R	missense_variant	CAS20and CAS17
		c.395A>T p.Tyr132Phe	Y132F	missense_variant	remaining 120 isolates
ERG3	B9J08_003737	c.202G>T p.Glu68*	E68*	stop_gained	CAS109
FKS1	B9J08_000964	c.1916C>A p.Ser639Tyr	S639Y	missense_variant	CAS109
	B9J08_000964	c.1916C>T p.Ser639Phe	S639F	missense_variant	CAS129 and CAS112
FKS2	B9J08_001020	c.2414G>A p.Trp805*	W805*	stop_gained	CAS1, CAS52, and CAS15
TAC1b	B9J08_004820	c.1747G>T p.Ala583Ser	A583S	missense_variant	CAS044, CAS3357, and CAS29
		c.575G>A p.Ser192Asn	S192N	missense_variant	CAS16
		c.1919C>T p.Ala640Val	A640V	missense_variant	CAS17 and CAS20
		c.1834C>T p.Gln612*	Q612*	stop_gained	CAS29
		c.2521_2523delTTC p.Phe841del	F841del	inframe_deletion	CAS12

reported *C. auris* clade 1 strains [28,32]. However, the impact and contribution of the indel (F841del) and stop codon (Q612*) on azole resistance remain to be investigated (Supplementary Data). Most of the *C. auris* isolates (79%, 22/28) also had reduced susceptibility to amphotericin B; however, the molecular mechanism of resistance to amphotericin B is not well understood. A recent report of a novel mutation in the *ERG6* was linked to amphotericin B resistance [32]. Some *Candida* species, such as *C. parapsilosis* and members of *C. lusitaniae* and *C. guilliermondii*, may be more resistant to AMB after azole exposure [33].

The abilities of *Candida auris* to acquire resistance to different antifungal drugs have been demonstrated using comparative genomes, and *in vitro*, and *in vivo* approaches [29,32,34–36]. The molecular mechanisms involve activation of efflux pumps due to mutations in transcription factors or upregulation of one of several genes involved in ergosterol synthesis [37,38]. Some of the unique mutations reported in this study may be associated with increased drug resistance, which could be due to microevolution and selection during prolonged treatment. All the Qatari isolates had substitutions in *ERG4* (M192I) and a silent mutation in *ERG5* (A870C) compared with the reference strain B8441. These mutations were not been reported previously. *ERG4* and *ERG5* are involved in fungal sterol biosynthesis. A nonsynonymous mutation in *ERG4* has been reported in *C. lusitaniae* isolates resistant to amphotericin B [39], while decreased sensitivity to polyenes was documented in clinical isolates of *Candida albicans* with alternation of *ERG5* [40]. The substitution and mutation in *ERG4* and *ERG5* may be linked to reduced susceptibility to amphotericin B in *C. auris*, although the impact of these mutations on structural changes and gene expression is not investigated. Recently, a substitution (A27T) in *CIS2*, encoding a γ-glutamyltranspeptidase, involved in detoxification of xenobiotics was linked to increased echinocandin MIC values in experimentally evolved *C. auris* strains [35]. *CIS2* (K74E) was reported in all susceptible and resistant isolates, suggesting this may represent a polymorphism not connected with resistance and may not be under selective pressure from antifungals. *SNQ2*, one of the ABC transporters, has been shown to contribute to azole resistance in *Candida glabrata* [41], and its expression raised azole resistance among Indian *C. auris* strains [42].

Isolate CAS109 was resistant to three classes of antifungal drugs with a unique disruption/mutation in *ERG3* (E68*) and *CDR2* (L1124P). A mutation (L207I) in *ERG3* encoding sterol Δ5,6-desaturase in addition to *ERG11*, may be linked to decreased susceptibility to amphotericin B [38]. The role of *CDR2*, an ABC-transporter-like *CDR1*, in azole resistance is less well characterized. There was no difference in *CDR2* expression between triazole-susceptible and -resistant *C. auris* strains [29], and no reduced susceptibilities were observed in CAS73 and CAS83, which also carried substitution L1124P in *CDR2*. The contribution of these mutations to azole resistance in Qatari *C. auris* would require further confirmation (e.g. Sanger sequencing) and functional validation.

One of the limitations was that we were not able to perform gene swapping experiments or sterol analyses to confirm the role of these unique mutations in drug resistance. Two isolates (CAS55 and CAS116) had higher MICs toward caspofungin. This could be attributed to the Eagle effect (paradoxical growth effect) for caspofungin [43] or upregulation of genes related to the synthesis of cell wall, ribosome, and cell cycle after exposure to caspofungin [44]. Similarly, *FKS2* is often linked to increased echinocandin resistance in *C. glabrata* [45]. However, the premature stop codon (W805*) reported in the three isolates did not appear to change the susceptibility to caspofungin, when we repeated the AST tests on two of the isolates (Table 1).

Candida auris represents a significant challenge to healthcare in Qatar because of multidrug resistance and high transmission fitness in a hospital environment. Based on AST data, most isolates had amphotericin B MICs ranging from 1 to 4 mg/L and were not susceptible to fluconazole (MIC ≥32 mg/L). As *C. auris* can be considered intrinsically resistant to fluconazole, micafungin (echinocandin) is recommended for the treatment of *C. auris* infections according to CDC guidelines (https://www.cdc.gov/fungal/candida-auris/c-auris-treatment.html). In our study, most isolates (75%, 21/28) were sensitive to echinocandins with higher prevalence of resistance than in the USA, where less than 5% of *C. auris* isolates have been reported as resistant to echinocandins. Pan-echinocandin resistance appears to be emerging, and this is alarming for physicians and infection control teams [16]. Evolution and emergence of resistance toward antifungals may lead to clinical

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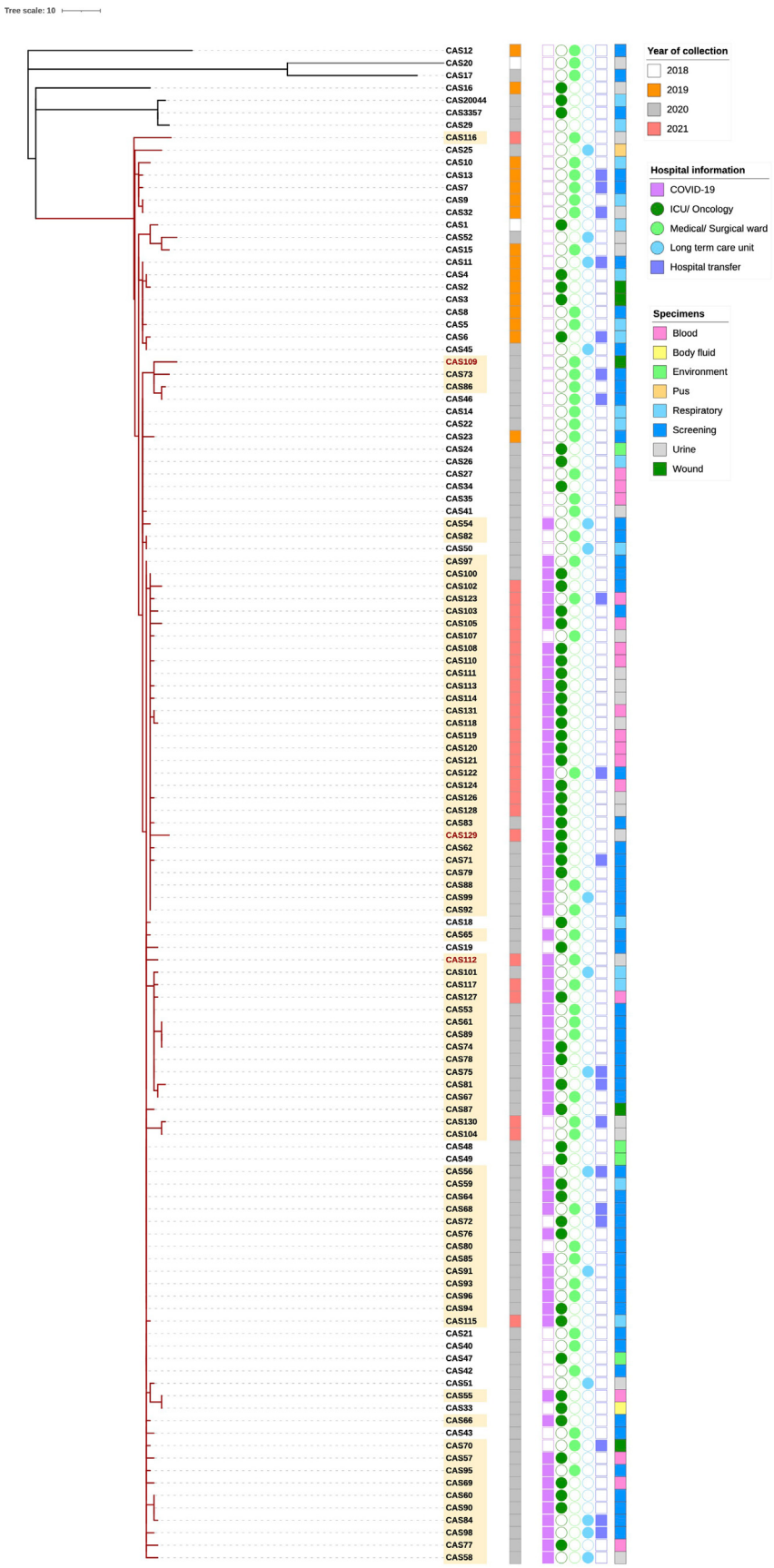

Fig. 1. Phylogenetic relationships of the 122 *Candida auris* isolates in Qatar. The tree was generated by FastTree and annotated in iTOL. Isolates sequenced in this study were highlighted in yellow. Year, source of isolation, and hospital information were annotated. The major circulating clone was highlighted in red. ICU, intensive care unit.

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failure during therapy [36]. Ongoing surveillance, screening, AST evaluation, and characterization of resistant genes and SNPs are required to determine the optimal management strategy of *C. auris* infection and transmission. Intensive disinfection efforts will be required to stop cross-transmission between healthcare institutions.

In conclusion, our study showed that all *C. auris* isolates from patients with COVID-19 belonged to the major circulating clone with low genetic variability and with ongoing transmission among various healthcare facilities in Qatar. The SNP data demonstrated the emergence of multidrug-resistant strains that carry novel mutations associated with enhanced resistance to azoles, amphotericin B, and echinocandins. Knowing the local epidemiology and susceptibility profiles of *C. auris* will help to guide infection control and patient therapy using the optimal empiric antifungal agents and allow better antimicrobial stewardship.

The raw sequencing reads are available from the National Center for Biotechnology Information under the accession number PRJNA693430.

Author contributions

Conceptualization: F.A. and C.T.; methodology: F.A., H.S., S.Salameh, and C.T.; investigation: F.A., H.S., S.Sundararaju, L.D., A.A., and C.T.; resources: H.S., E.I., A.A., P.T., and S.Salameh; formal analysis: F.A., H.S., S.Sundararaju, and C.T.; writing—original draft: F.A., H.S., and C.T.; writing—review and editing: all authors; supervision: M.A., P.T., A.P.-L., and C.T.; funding acquisition: F.A., S.Salameh, P.T., A.P.-L., and C.T.

Transparency declaration

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.04.025.

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